

Panadeine[®] Extra Tablets

Paracetamol 500mg, Codeine Phosphate 15mg

Presentation

Capsule-shaped tablets (white, marked PAN 15): 12s and 24s (retail pack) and 6s (health professional sample pack).

Each tablet contains 500 mg of paracetamol and 15 mg codeine phosphate.

Uses

Actions

Pharmacodynamics

Paracetamol is a para-aminophenol derivative that exhibits analgesic and anti-pyretic activity. It does not possess anti-inflammatory activity. It is given by mouth or rectally for mild to moderate pain and fever.

Codeine phosphate is an opioid analgesic which binds with stereospecific receptors at many sites within the central nervous system. It alters processes affecting both the perception of pain and the emotional response to pain. Codeine has about one-sixth of the analgesic activity of morphine.

Pharmacokinetics

Paracetamol

After oral administration, paracetamol is absorbed rapidly and completely from the small intestine; peak plasma levels occur 30 to 120 minutes after administration. Paracetamol is uniformly distributed throughout most body fluids; the apparent volume of distribution is 1 to 1.2 L/kg.

Paracetamol can cross the placenta and is excreted in milk. Plasma protein binding is negligible at usual therapeutic concentrations but increases with increasing concentrations.

Paracetamol is metabolised by the hepatic microsomal enzyme system. In adults at therapeutic doses, paracetamol is mainly conjugated with glucuronide (45-55%) or sulfate (20-30%). A minor proportion (less than 20%) is metabolised to catechol derivatives and mercapturic acid compounds via oxidation. Paracetamol is metabolised differently by infants and children compared to adults, the sulfate conjugate being predominant.

Paracetamol is excreted in the urine mainly as the glucuronide and sulphate conjugates. Less than 5% is excreted as unchanged paracetamol with 85-

90% of the administered dose eliminated in the urine within 24 hours of ingestion. The elimination half-life varies from 1 to 4 hours. Food intake delays paracetamol absorption.

Codeine

Codeine has about one-sixth of morphine's analgesic activity. It is well absorbed from the gastrointestinal tract and does not interfere with paracetamol absorption.

It is metabolised in the liver to morphine and norcodeine, which with codeine, are excreted in the urine, partly as conjugates with glucuronic acid. Excretion is almost complete within 24 hours.

Patients who metabolise drugs poorly via CYP2D6 are likely to obtain reduced benefit from codeine due to reduced formation of the active metabolite. This may be the case in about 8% of patients.

Indications

Temporary relief of moderate to severe acute pain associated with strong headaches, migraine headaches, dental surgery or toothache, menstrual pain and sports injuries (eg. backaches and muscular pain).

Dosage and Administration

Adults and Children over 12 years:

2 caplets four times a day if required (maximum 8 caplets in 24 hours).

Not recommended for children under 12 years of age.

Do not exceed the stated dose. Should not be used with other paracetamol or codeine containing products. If symptoms persist or worsen medical advice must be sought.

Contraindications

- Known sensitivity to paracetamol, codeine or any of the other ingredients.
- Acute alcoholism.
- Patients at risk of paralytic ileus
- Hepatic failure

- Mothers who are breastfeeding, unless prescribed by a doctor.

Warnings and Precautions

Panadeine Extra should be used with caution in patients with the following conditions:

- Impaired kidney/liver function
- Gall bladder disease or gall stones
- Recent gastro-intestinal surgery
- Obstructive and inflammatory bowel disease- codeine reduces peristalsis, increases tone and segmentation in the bowel and can raise colonic pressure
- Patients taking monoamine oxidase inhibitors or within 14 days of stopping such treatment.

Codeine is an addictive substance; prolonged or excessive use of high doses of codeine may produce dependence. Stopping treatment can result in withdrawal symptoms. Codeine is not a satisfactory substitute for patients dependent on morphine. Regular use of analgesics for headache can result in an overuse syndrome.

Abrupt withdrawal precipitates a withdrawal syndrome. Symptoms may include tremor, insomnia, restlessness, irritability, anxiety, depression, anorexia, nausea, vomiting, diarrhoea, sweating, lacrimation, rhinorrhoea, sneezing, yawning, piloerection, mydriasis, weakness, pyrexia, muscle cramps, dehydration and increase in heart rate, respiratory rate and blood pressure. These effects can also occur in neonates exposed to codeine in utero (see use in pregnancy).

Tolerance diminishes rapidly after withdrawal so a previously tolerated dose may prove fatal.

Genetic polymorphism - Codeine is metabolised to morphine by cytochrome P450 2D6. Some patients are ultra-rapid metabolisers and are at higher risk of toxic opioid effects. Some patients are slow metabolisers and these patients may not experience adequate analgesic effect with codeine.

Panadeine Extra is for the relief of minor and temporary ailments and should be used strictly as directed. Prolonged use without medical supervision could be harmful.

Keep out of sight and reach of children.

Do not use for more than 3 days without medical advice.

Use in Pregnancy & Lactation

Category A - Drugs which have been taken by a large number of pregnant women and women of childbearing age without any proven increase in the frequency of malformations or other direct or indirect harmful effects on the foetus having been observed.

Panadeine may be used during pregnancy on the advice of a doctor. However, it is recommended that non-drug therapies such as rest and massage are tried first.

The balance of benefits and risks should be carefully considered because opioid analgesics cross the placenta. Regular use during pregnancy may cause physical dependence in the foetus, leading to withdrawal symptoms (convulsions, irritability, excessive crying, tremors, hyperactive reflexes, fever, vomiting, diarrhoea, sneezing and yawning) in the neonate. Prolonged high dose use of codeine prior to delivery may produce codeine withdrawal symptoms in the neonate.

Paracetamol is excreted in breast milk. Peak concentrations of 10 to 15 mcg/mL have been measured within 1 to 2 hours of a single 650 mg maternal dose. The half life of paracetamol in breast milk is 1.35 to 3.5 hours. Neither paracetamol or its metabolites were detected in the urine of breastfed infants following the maternal 650 mg dose.

Codeine is excreted into breast milk. However with usual analgesic doses, concentrations are generally low.

Infants of nursing mothers taking codeine may have an increased risk of morphine overdose if the mother is an ultra-rapid metaboliser of codeine. Nursing mothers taking codeine who are ultra-rapid metabolisers, may have higher morphine levels in their breast milk, which may lead to life-threatening or fatal side effects in nursing babies.

Signs of high morphine levels in a mother are extreme sleepiness and trouble caring for the baby.

Breastfed babies usually nurse every two or three hours and should not sleep more than 4 hours at a time. If the baby shows signs of increased sleepiness (more than usual), difficulty in breastfeeding, breathing difficulties, or limpness, the mother should seek medical advice immediately.

Codeine-containing products must not be used while breastfeeding unless prescribed by a doctor. The lowest effective dose should be used for the shortest possible time. Nursing monitors should be informed after carefully monitoring the infant during treatment for any signs or symptoms of morphine toxicity as described above.

Use in children

Not recommended for children below age 12.

Use in the elderly

Elderly patients may be more susceptible to the effects, especially the respiratory depressant effects of these medications. Also elderly patients are more likely to have prostatic hypertrophy or obstruction and age-related renal function impairment, and are therefore more likely to be adversely affected by opioid-induced urinary retention. The risk of constipation and faecal impaction is also greater in the elderly.

Elderly patients may metabolise or eliminate opioid analgesics more slowly than younger adults. Lower doses or longer dosing intervals than those usually recommended for adults may be required, and are usually therapeutically effective for these patients.

Effects on ability to drive and use machines

Codeine may cause drowsiness or a decrease in alertness in some patients. Patients should be cautioned about operating vehicles or machinery, or engaging in activities which require them to be fully alert.

Interactions

Possible interactions include:

- Warfarin and other anticoagulants
- Monoamine Oxidase Inhibitors – due to the possible risk of excitation or depression,
- avoid concomitant use and for 14 days after discontinuation of MAOI.
- Alcohol enhanced sedative and hypotensive effect, increased risk of respiratory depression
- Hypnotics and anxiolytics – enhanced sedative effect, increased risk of respiratory depression
- Metoclopramide and domperidone – antagonistic effect on GI activity
- Anaesthetics – enhanced sedative and hypotensive effect
- Tricyclic antidepressants – enhanced sedative effect
- Antipsychotics – enhanced sedative and hypotensive effect

Adverse Effects

Adverse events from historical clinical trial data are both infrequent and from small patient exposure. Accordingly, events reported from extensive post-marketing experience at therapeutic/labelled dose and considered attributable

are tabulated below by System Organ Class and frequency. Frequencies are defined as: very common (>1/10), common (>1/100, <1/10), uncommon (>1/1000, <1/100), rare (>1/10,000, <1/1000) and very rare (<1/10,000) including isolated reports.

Paracetamol:

Reports of adverse reactions to paracetamol are very rare.

Blood and lymphatic system disorders: thrombocytopenia

Immune System disorders: Anaphylaxis; cutaneous hypersensitivity reactions including skin rashes, angioedema and Stevens Johnson syndrome

Respiratory, thoracic and mediastinal disorders: Bronchospasm

Hepatobiliary disorders: hepatic dysfunction

Codeine:

Adverse reactions for codeine may depend on dose and individual patient metabolism. Some patients are more likely to experience undesirable effects because they rapidly convert codeine to morphine.

The following adverse reactions have been reported (unknown frequency):

Immune system disorders - rash, urticaria, pruritus, increased sweating, redness of flushed face, angioedema.

Nervous system disorders – drowsiness, malaise, tiredness, vertigo, dizziness, worsening of headache with prolonged use.

Gastrointestinal Disorders - constipation, dyspepsia, biliary spasm, nausea, vomiting, dry mouth, acute pancreatitis in patients with a history of cholecystectomy.

Withdrawal effects - abrupt withdrawal of codeine precipitates a withdrawal syndrome. Symptoms may include tremor, insomnia, restlessness, irritability, anxiety, depression, anorexia, nausea, vomiting, diarrhoea, sweating, lacrimation, rhinorrhoea, sneezing, yawning, piloerection, mydriasis, weakness, pyrexia, muscle cramps, dehydration and increase in heart rate, respiratory rate and blood pressure.

Tolerance diminishes rapidly after withdrawal so a previously tolerated dose may prove fatal.

Regular prolonged use of codeine is known to lead to addiction and tolerance. Prolonged use of a painkiller for headaches can make them worse.

Overdosage

Accidental overdose is usually rare due to the high therapeutic index of the product.

Paracetamol overdose can result in severe liver damage and sometimes acute renal tubular necrosis.

Toxic symptoms of paracetamol overdose include vomiting, abdominal pain, hypotension, sweating, central stimulation with exhilaration and convulsions in children, drowsiness, respiratory depression, cyanosis and coma.

In adults, hepatotoxicity may occur after ingestion of a single dose of paracetamol 10 to 15 g (20 to 30 tablets or 10 to 15 times the normal dose); a dose of 25 g (50 tablets) or more is potentially fatal.

Symptoms during the first two days of acute poisoning by paracetamol do not reflect the potential seriousness of the intoxication. Major manifestations of liver failure such as jaundice, hypoglycaemia and metabolic acidosis may take at least three days to develop.

Treatment

Prompt treatment is essential even when there are no obvious symptoms.

In cases of over dosage, methods of reducing absorption of ingested drug are important. Prompt administration of activated charcoal 50 g in 150 mL of water and 150 mL sorbitol 50% solution by mouth may reduce absorption. It is recommended that intravenous fluids such as Normal Saline be given concurrently. Gastric lavage is indicated if the patient is unwilling or unable to drink an activated charcoal/sorbitol mixture.

If the history suggests that paracetamol 15 g or more has been ingested, administer the following antidote:

Intravenous acetylcysteine 20%: Administer acetylcysteine immediately without waiting for positive urine test or plasma level results if 8 hours or less since overdose ingestion. Initial dose 150 mg/kg over 15 minutes, followed by continuous infusion of 50 mg/kg in glucose 5% 500 mL over four hours and 100 mg/kg in glucose 5% 1 L over 16 hours.

If more than 8 hours have elapsed since the over dosage was taken, the antidote may be less effective.

Pharmaceutical Precautions

Store below 30°C.

Keep out of reach of children.

Shelf life of the product is 3 years from the date of manufacture.

Medicine Classification

PHARMACIST ONLY MEDICINE

Package Quantities

Blister packs of 12, 24, 6 (healthcare professional sample) caplets.

Further Information

Excipients

- Maize Starch
- Purified Talc
- Pregelatinised Maize Starch
- Povidone
- Stearic Acid
- Potassium Sorbate
- Magnesium Stearate

It contains no sugar, lactose or glucose.

Name and Address

GlaxoSmithKline (NZ) Ltd
trading as GlaxoSmithKline Consumer Healthcare
8th Floor, AMP Centre, cnr Customs & Albert Sts
Auckland

Telephone: (09) 367 2970

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